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Brown-Vialetto-Van Laere Syndrome in a Large Inbred Lebanese Family: Confirmation of Autosomal Recessive Inheritance?

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Brown-Vialetto-Van Laere syndrome or pontobulbar palsy with deafness is a rare disorder characterized by bilateral nerve deafness, a variety of cranial nerve disorders usually involving the motor components of the 7th and 9th to 12th cranial nerves, and less commonly an involvement of spinal motor nerves and upper motor neurons. Familial and sporadic cases have been reported. Based on particular evidence, autosomal recessive, autosomal dominant, and X-linked inheritance, as well as autoimmune origin have been considered. We report on a large inbred Lebanese family with four patients of both sexes, strongly suggesting autosomal recessive inheritance. Am. J. Med. Genet. 92:117–121, 2000.

KEY WORDS: autosomal recessive; Brown-Vialetto-Van Laere syndrome; consanguinity; deafness; pontobulbar palsy

INTRODUCTION

Pontobulbar palsy with deafness, known as the Brown-Vialetto-Van Laere (BVVL) syndrome (MIM 211530), is a rare disorder characterized by bilateral nerve deafness of slow or rapid onset, accompanied or followed by a variety of cranial nerve disorders usually involving the motor components of the 7th and 9th to 12th cranial nerves, and less commonly spinal motor nerves, and upper motor neurons. Since the first description by Brown [1894], about 35 cases have been reported [Abarbanel et al., 1991; Alberca et al., 1980; Arnould et al., 1968; Ben Hamida and Hentati, 1984; Boudin et al., 1971; Brucher et al., 1981; Davenport and Mumford, 1994; De Mattos et al., 1982; De Oliveira et al., 1995; Francis et al., 1993; Gallai et al., 1981; Hawkins et al., 1990; Lombaert et al., 1976; Orrel et al., 1997; Piccolo et al., 1992: Serratrice and Gastaut, 1972; Sztajzel et al., 1998; Trillet et al., 1970; Van Laere, 1966, 1967, 1977; Vialetto, 1936]. Half of those were familial with no recognized symptoms in parents or other relatives, suggesting autosomal recessive inheritance. In two families autosomal dominant inheritance with variable penetrance and expressivity, and alternatively X-linked inheritance, were postulated [Van Laere, 1967; Hawkins et al., 1990]. All other cases were sporadic, one of which had a moderate elevation of antiganglioside GM1 antibodies also suggesting a possible autoimmune origin [Sztajzel et al., 1998].

We describe three children with severe features of the BVVL syndrome, in a large inbred family. To our knowledge, this is the first report of a consanguineous family with such a presentation. The different modes of inheritance are discussed.

MATERIAL AND METHODS

This kindred (Fig.1) resides in northern Lebanon and belongs to the Shiite Muslim community.

Case 1 (VI-8, Fig.1), is the propositus. When he was born, the father was 34 and the mother 24 years old. Gestation was unremarkable and the baby was delivered by cephalic presentation at 40 weeks. His weight was 3600 g. His neonatal course was uncomplicated and early motor development was normal. He sat up at 7 months, started to walk at 11 months, and said some words at 14 months. At the age of 2-1/2, his parents noted that his hearing and walking were becoming progressively impaired, with weight loss. Two years later,

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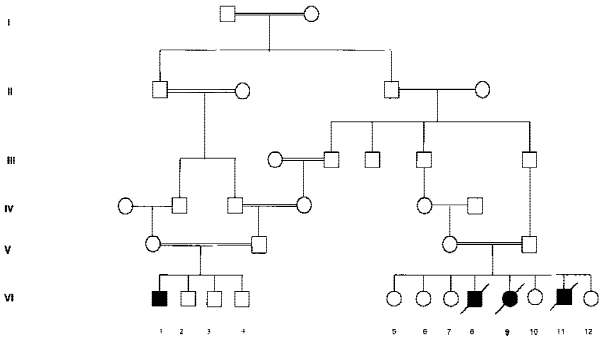

Fig. 1. Pedigree of the family.

he was completely deaf, shouting some words, and could no longer walk without support.

We first examined him at the age of 8 years. The general appearance was that of a weak and slender boy. He was totally deaf, hypotonic, unable to hold his head erect, and could walk only a few yards with support. Otherwise, he seemed to be of normal intelligence. His weight was 21 kg (5th centile), length 129 cm (60th centile), and occipitofrontal circumference (OFC) 52 cm (50th centile). The neurological examination revealed axial and appendicular hypotonia; dorsal scoliosis; tongue fasciculation, paucity of spontaneous movements; important muscular weakness involving muscles of neck, shoulders, and upper arms with major muscular wasting; clawed hands with thenar and hypothenar amyotrophy; absent deep tendon reflexes; and no Babinski response (Fig. 2). There was no ptosis, no motor ocular movement impairment, and a normal thoracic expansion without paradoxical movements. This presentation evoked a bulbar dysfunction with cranial nerve impairments associated with motor neuron signs.

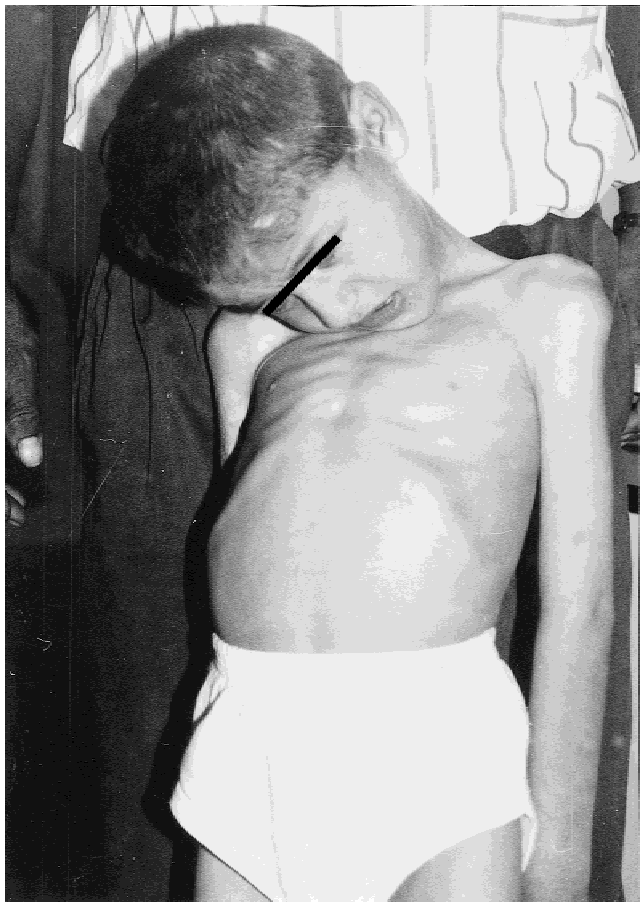

Fig. 2. Photograph of case 1 at 8 years. Note the appendicular hypotonia, the important muscular weakness involving muscles of the neck, shoulders, and upper arms with major muscular wasting.

Radiological examination of the skeleton revealed a left curved scoliosis, and thin diaphyses of the long bones. Magnetic resonance imaging (MRI) of the brain and cervical spine were normal, as were abdominal and cardiac ultrasonography. Brainstem auditory responses were completely absent. Complete blood count; hemoglobin electrophoresis; serum electrolytes; blood glucose levels; triglycerides; cholesterol; amino acid studies of plasma and urine; urinalysis; thyroid; liver and renal function tests; lactate; plasma very long chain fatty acid; muscle enzymes; and white blood cell enzyme assay screening were all unremarkable. Slightly elevated pyruvate level was noted. Karyotyping (high resolution G- and R-banding) was normal 46,XY. This child died at 11 years, most probably from acute respiratory failure. No autopsy was performed.

Case 2 (VI-11, Fig.1) was born five years after his affected brother. Gestation and delivery by cephalic presentation at 40 weeks were unremarkable. Birth weight was 2900 g (60th centile). The clinical history was quite similar to that of his affected brother. We first saw him at age 7. Weight was 18 kg (5th centile), length 120 cm (35th centile), and OFC of 51 cm (25th centile). He was alert and awake with minimal reaction to vocal sounds, and his speech limited to minimal vocalization. Physical examination disclosed a slender boy with diffuse muscular wasting and a mild kyphoscoliosis with a right gibbosity. He was unable to hold his head erect and maintain a sitting position on his own (Fig. 3 a,b). The neck veins were distended, the sternocleidomastoid, intercostal, and distal and proximal limb muscles were markedly wasted. There were contractures of the flexors of the fingers with complete impairment of manual dexterity. The chest expansion was limited and paradoxical respiration was noted. A protuberant abdomen with a liver edge 3 cm below the right costal margin was noted, but without splenomegaly. The neurological exam revealed a bilateral facial paresis with poor smile and inability to close the eyes tightly; atrophic tongue with fasciculation; poor gag reflexes; truncal and appendicular hypotonia; symmetrically weak motor strength with inability to move the upper arms against gravity; fine twitching of the fingers and toes; and absent deep tendon reflexes with no plantar reflexes. Nystagmus and abnormal eye motility and pupillary reflexes were absent. His sensory exam to pinprick and light touch seemed equally intact. Anal tone was present. The parents reported that he had dysphagia for liquids and occasionally to solids, with episodes of choking and coughing, and intermittently short episodes of cyanosis. Ophthalmologic examination was normal. ECG showed a tachycardia of 115

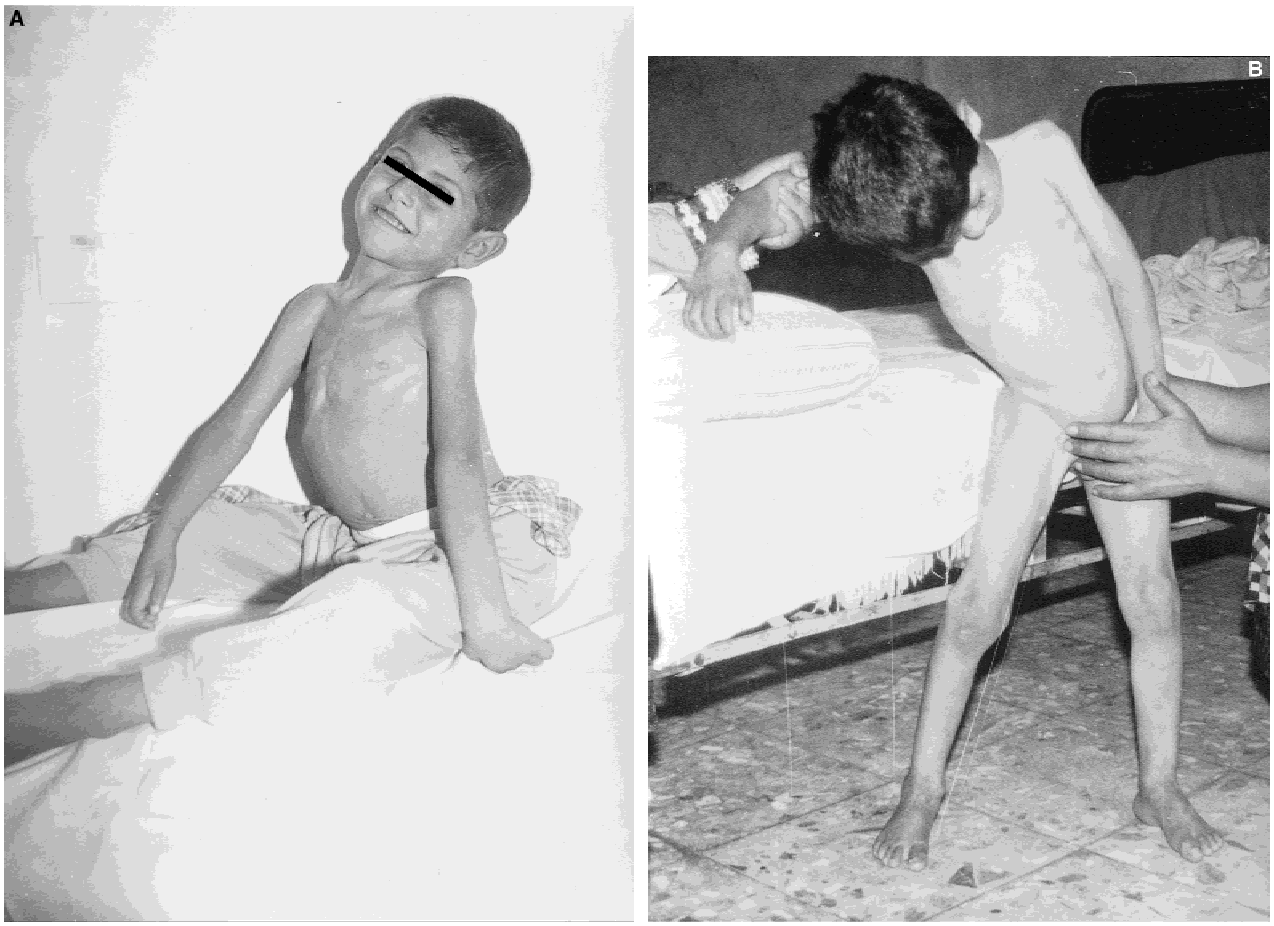

Fig. 3. Photograph of case 2 at 7 years showing the resemblance to case 1. Note the diffuse muscular wasting and the clawed hands.

beats/min and incomplete right branch block. EEG was unremarkable. The evoked potential revealed a severe neurosensory hearing loss.

Needle electromyography was neurogenic and showed fibrillation activity particularly at the upper arms. Motor velocities were normal. The sensitive velocities were incalculable because it was not possible to obtain sensitive potentials.

All other laboratory and radiological exams were identical to those of his affected brother. He died suddenly after 4 months. No autopsy was performed.

Physical examinations of the parents and their other children were completely normal, with the exception of one daughter (VI-9, Fig.1) who supposedly presented with exactly the same problems as her affected brothers. She died at the age of 4 years following a severe episode of gastroenteritis.

Case 3 (VI-1, Fig.1) was born at term after an uncomplicated pregnancy. According to the parents, motor milestones were achieved within normal limits. The clinical course was identical to that of the other affected members of the family except that his hearing and neurological problems started a little later at (3-1/2 years of age). On examination, at age 6-1/2, weight was 20 kg (25th centile), length 117 cm (50th centile), and OFC 52 cm (50th centile). He was completely deaf, could walk slowly when leaning on something, but was weak in all movements, particularly those of the neck and hands. Neurological examination showed identical results as those of his affected cousins, except that muscle wasting was less marked, and there were no fasciculations of the extremities. Auditory brainstem studies disclosed a severe neurosensory hearing loss. Nerve conduction and electromyogram studies revealed an absence of sural and sensory median potentials, but normal motor velocities. Nerve biopsy and MRI were not performed. The search for *SMN* and *NAIP* mutations was negative. All other investigations, including the radiological ones, were unremarkable.

DISCUSSION

The presence of deafness associated with progressive involvement of cranial nerves, neurogenic muscular atrophy, and respiratory difficulties in the four children described here is consistent with the diagnosis of BVVL syndrome. This syndrome is part of the large group of disorders of the motor neuron system affecting anterior horn cells. The early age of onset, deafness, early involvement of bulbar nuclei, and absence of pyramidal signs distinguish it from amyotrophic lateral sclerosis. Progressive muscular atrophy and spinal muscular atrophy do not show neural deafness, and present with lower motor neuron signs only. Progressive hereditary bulbar paralysis of Fazio-Londe (MIM 211500) re-

sembles BVVL syndrome except for the progressive deafness and loss of vestibular responses. The Nathalie syndrome, characterized by spinal muscular atrophy and sensorineural hearing loss, also includes cataracts, cardiac conduction disorders, and hypogonadism not reported in BVVL syndrome [Cremers et al., 1975]. The Boltshauser syndrome is very close to BVVL syndrome, although brainstem signs are restricted to vocal cord paralysis, and the inheritance is likely to be autosomal dominant [Boltshauser et al., 1989]. Finally, the Madras disease [Meenakshisundaram et al., 1970] is also very close and could be the same disorder [Summers et al., 1987]. Nevertheless, the latest reported cases were sporadic, showing a possible environmental—viral or autoimmune—origin, and the clinical course seems benign [Gourie-Devi and Suresh, 1988].

To date, nearly 35 cases of BVVL syndrome have been reported in the literature [Abarbanel et al., 1991; Alberca et al., 1980; Arnould et al., 1968; Ben Hamida and Hentati, 1984; Boudin et al., 1971; Brucher et al., 1981; Davenport and Mumford, 1994; De Mattos et al., 1982; De Oliveira et al., 1995; Francis et al., 1993; Gallai et al., 1981; Hawkins et al., 1990; Lombaert et al., 1976; Orrel et al., 1997; Piccolo et al., 1992; Serratrice and Gastaut, 1972; Sztajzel et al., 1998; Trillet et al., 1970; Van Laere, 1966, 1967, 1977; Vialetto, 1936]. The age of onset is usually in the second decade, and the disease course is slowly progressive. Our family is the first one to show affected siblings that present the same severe features: deafness and pontobulbar palsy between 2 and 4 years, with rapid deterioration. Only seven cases have been reported with symptoms beginning within the first decade [Arnould et al., 1968; Gallai et al., 1981; Van Laere, 1966; Vialetto, 1936]; in one of these, early death was reported [Gallai et al., 1981: case 2]. The latter was the brother of an affected girl who became symptomatic at 2 years, but the disease had a slow progression. Since neither the age of onset, nor the time elapsed between the beginning of the hearing loss and that of neurological problems predispose to the severity of the disease, we cannot define basic criteria to assess the gravity of this disease. The intra- and interfamilial variability reported in the familial cases could be explained either by allelic or nonallelic heterogeneity or by other factors in the genetic or environmental background.

The nerve conduction studies performed on cases 2 and 3 disclosed the absence of sensory responses, showing that this syndrome could be classified as a severe sensorimotor neuropathy rather than a pure motor neuropathy or anterior horn cell disorder. Unfortunately, nerve biopsy (case 3) or autopsy (case 1 and 2) were not accepted by the parents to clarify this. Previous sural nerve biopsy studies revealed slight depletion of nerve fibers [Gallai et al., 1981], or normal fibers [Hawkins et al., 1991; Lombaert et al., 1976].

The mode of inheritance of this rare entity is still not completely determined. In the previous report, the sex ratio was 1:5 showing preponderance of females among recorded cases [Sztajzel et al., 1998]. This sex ratio rate was even lower in familial cases. It was suggested that males were more severely affected, and tend to die earlier in life and remain undiagnosed [Hawkins et al., 1990]. In one family, hearing loss was present on both sides of the family [Van Laere, 1967]. In another family, different members were affected by all or some of the features of the BVVL syndrome, suggesting an autosomal dominant inheritance with variable expressivity and sex-related expression, or even an X-linked inheritance [Hawkins et al., 1990]. The family reported here is the first in which the parents are consanguineous (Table I). Three boys were affected and one girl who died early in life. The pedigree is not compatible with X-linked inheritance (Fig. 1). Thus, data on this family strongly suggest an autosomal recessive form of inheritance for the condition. The absence of the report of any consanguineous family and the presence of an important number of sporadic cases could be explained by de novo rearrangements of an autosomal recessive gene: a mutated allele present in one of the parents, and a de novo mutation on the second allele coming from the other parent. This phenomenon has already been reported in different autosomal recessive diseases such as spinal muscular atrophy [Wirth et al., 1997], a close but distinct syndrome from the BVVL. Nevertheless, other modes of transmission still might be hypothesized. For example, mutations in different parts of a gene might be able to produce quite close phenotypes but with a different mode of transmission, as has been reported for the *PMP22* gene, for example Parman et al., 1999. Thus, a proportion of sporadic BVVL syndrome, assumed to be recessive, might result from a de novo dominant mutation.

In conclusion, we have reported on the first consanguineous family of BVVL syndrome with a severe form. The etiopathogenesis of this disease is still unknown. Two patients tested for mutations in the *SMN* and *NAIP* genes on chromosome 5q11.2-13.3, were normal

TABLE I. Clinical Summary of the Patients With Family Histories of Brown-Vialetto-Van Laere Syndrome*

Authors	Family	Patients' sex	Age of onset of deafness (y)	Age of onset of cranial palsies (y)	Severity	Death (y)	Other cases	Consanguinity	Inheritance
Present report	1	3 M	2 1/2	2 1/2	+	11–7	1 F	+	AR
Vialetto, 1936	1	1 F	16	35	–	–	3 F	–	AR
	2	1 F	0	30	–	–	9 sibs?	–	?
Van Laere, 1966	1	1 F	10	10		–	4 F	–	AR
Van Laere, 1967	1	1 M	13	20	–	–	FD	–	AD?
Boudin et al., 1971	1	2 F	11 and 14	?	–	–	–	–	AR
Lombaert et al., 1976	1	1 M/1 F	Child/17	?/25	+/+	19/25	–	–	AR
Gallai et al., 1981	1	1 M/1 F	2/1 1/2	14/1 1/2	–/+	–/2		–	AR
Hawkins et al., 1991	1	1 F	12	13	+	17 1/4	1 Aunt; FD	–	AD; XL?
Davenport and Mumford, 1994	1	1 F	Child	18	±	–	Mother	–	AD

*M = male; F = female; y = years; FD = familial deafness; AR = autosomal recessive; AD = autosomal dominant; XL = X-linked.

[Orrel et al., 1997; Present report: case 3]. Identification of the gene by a whole genome screening is likely to provide more information about the pathogenesis. Pooling such families worldwide is the only chance to achieve it. The theoretical lod score, calculated by computer simulation methods, is above 3, showing evidence for the informativity of our pedigree. Thus, the localization of the gene in this family will help us better understand this rare entity, and differentiate it or not from the other close syndromes.

REFERENCES

Abarbanel JM, Ashby P, Marquez-Julio A, Chapman KR. 1991. Bulbopontine paralysis with deafness: the Vialetto-Van Laere syndrome. Can J Neurol Sci 18:349–351.

Alberca R, Montero C, Ibanez A, Segura DI, Miranda-Nieves G. 1980. Progressive bulbar paralysis associated with neural deafness—a nosological entity. Arch Neurol 37:214–221.

Arnould G, Tridon P, Laxenaire M, Picard L, Weber M, Brichet B. 1968. Paralysie bulbo-pontine chronique progressive avec surdité—A propos d'une observation de syndrome de Fazio-Londe. Rev Oto-Neuro-Ophtal 40:158–161.

Ben Hamida M, Hentati F. 1984. Maladie de Charcot et sclérose latérale amyotrophique juvénile. Rev Neurol 140:202–206.

Boltshauser E, Lang W, Spillmann T, Hof E. 1989. Hereditary distal muscular atrophy with vocal cord paralysis and sensorineural hearing loss. A dominant form of spinal muscular atrophy? J Med Genet 26:105–108.

Boudin G, Pépin B, Vernant JC, Gautier B, Gouérou B. 1971. Cas de paralysie bulbo-pontine chronique progressive avec surdité. Rev Neurol (Paris) 124:90–92.

Brown CH. 1894. Infantile amyotrophic lateral sclerosis of the family type. J Nerv Ment Dis 21:707–716.

Brucher JM, Dom R, Lombaert A, Carton H. 1981. Progressive pontobulbar palsy with deafness. Clinical and pathological study of two cases. Arch Neurol 38:186–190.

Cremers C, Ter Haar BG, Van Rens TJ. 1975. The Nathalie syndrome. A new hereditary syndrome. Clin Genet 8:330–340.

Davenport RJ, Mumford CJ. 1994. The Brown-Vialetto-Van Laere syndrome: a case report and literature review. Eur J Neurol 1:51–54.

De Mattos JP, de Lima JM, de Amorim AC, Aterino Filho C, Lima AL. 1982. Esclerose lateral amiotrofica com surdez: relato de um caso e revisao da literatura. Arq Neuropsiquiatr 40:201–207.

De Oliveira JT, Moreira PR, Cardoso F, Perpetuo FO. 1995. Brown-Vialetto-Van Laere syndrome: report of 2 cases. Arq Neuropsiquiatr 53:789–791.

Francis DA, Ponsford JR, Wiles CM, Thomas PK, Duchen LW. 1993. Brown-Vialetto-Van Laere syndrome. Neuropathol Appl Neurobiol 19: 91–94.

Gallai V, Hockaday JM, Hughes JT, Lane DJ, Oppenheimer DR, Rushworth G. 1981. Ponto-bulbar palsy with deafness (Brown-Vialetto-Van Laere syndrome). A report on three cases. J Neurol Sci 50:259–275.

Gourie-Devi M, Suresh TG. 1988. Madras pattern of motor neuron disease in South India. J Neurol Neurosurg Psychiatry 51:773–777.

Hawkins SA, Nevin NC, Harding AE. 1990. Pontobulbar palsy and neurosensory deafness (Brown-Vialetto-Van Laere syndrome) with possible autosomal dominant inheritance. J Med Genet 27:176–179.

Lombaert A, Dom R, Carton H, Brucher JM. 1976. Progressive pontobulbar palsy with deafness—a clinico-pathological study. Acta Neurol Belg 76:309–314.

Meenakshisundaram F, Jagannathan K, Ramamurthy B. 1970. Clinical pattern of motor neuron disease seen in younger age groups in Madras. Neurology (India) 18(suppl 1):109–112.

Orrel RW, Habgood JJ, Belleroche de JS, Lane RJM. 1997. The relationship of spinal muscular atrophy to motor neuron disease: investigation of *SMN* and *NAIP* gene deletions in sporadic and familial ALS. J Neurol Sci 145:55–61.

Parman Y, Plante-Bordeneuve V, Guiochon-Mantel A, Eraksoy M, Said G. 1999. Recessive inheritance of a new point mutation of the PMP-22 gene in Dejerine-Sottas disease. Ann Neurol 45:518–522.

Piccolo G, Marchioni E, Maurelli M, Simonetti F, Bizzetti F, Savoldi F. 1992. Recovery from respiratory muscle failure in a sporadic case of Brown-Vialetto-Van Laere syndrome with unusually late onset. J Neurol 239:355–356.

Serratrice G, Gastaut JL. 1972. Amyotrophies degeneratives et lésions du neurone moteur (à propos de 32 observations). Marseille Med 109:821–840.

Summers BA, Swash M, Schwartz MS, Ingram DA. 1987. Juvenile-onset bulbospinal muscular atrophy with deafness: Vialetto-Van Laere syndrome or Madras-type motor neuron disease? J Neurol 234:440–442.

Sztajzel R, Kohler A, Reichart M, Djientcheu VP, Chofflon M, Magistris MR. 1998. Syndrome de Brown-Vialetto-Van Laere. Un cas avec anticorps anti-ganglioside GM1 et revue de la littérature. Rev Neurol (Paris) 154:51–54.

Trillet M, Girrard PF, Schott B, Ramel P, Woehrle R. 1970. La paralysie bulbo-pontine chronique progressive avec surdité (à propos d'une observation clinique). Lyon Med 223:145–153.

Van Laere J. 1966. Paralysie bulbo-pontine chronique progressive familiale avec surdité. Un cas de syndrome de Klippel-Trenaunay dans la même fratrie. Problèmes diagnostics et génétiques. Rev Neurol 115: 289–295.

Van Laere J. 1967. Over een nieuw geval van chronische bulbopontiene paralysis met doofheid. Verh Vlaam Akad Geneesk Belg 30:288–308.

Van Laere J. 1977. Un nouveau cas de paralysie bulbo-pontine chronique progressive avec surdité. Rev Neurol (Paris) 33:119–124.

Vialetto E. 1936. Contibuto alla forma ereditaria della paralisi bulbare progressiva. Riv Sper Freniat 40:1–24.

Wirth B, Schmidt T, Hahnen E, Rudnik-Schoneborn S, Krawczak M, Muller-Myhsok B, Schonling J, Zerres K. 1997. De novo rearrangements found in 2% of index patients with spinal muscular atrophy: mutational mechanisms, parental origin, mutation rate, and implications for genetic counseling. Am J Hum Genet 61:1102–1111.